AAC Journals.ASM.org

High-Dose Continuous Oxacillin Infusion Results in Achievement of Pharmacokinetics Targets in Critically Ill Patients with Deep Sternal Wound Infections following Cardiac Surgery

Nicolas Nesseler,[a,b,c] Marie-Clémence Verdier,[c,d] Yoann Launey,[a,b,c] Alexandre Malherbe,[a,c] Marine Dermu,[c,d] Caroline Piau,[c,e] Erwan Flécher,[c,f] Olivier Tribut,[g] Yannick Mallédant,[a,b,c] Philippe Seguin[a,b,c]

Service de Réanimation Chirurgicale, Pôle Anesthésie-SAMU, Urgences, Réanimations (ASUR), Hôpital Pontchaillou, Rennes, France[a]; INSERM U991, Hôpital Pontchaillou, Rennes, France[b]; Université Rennes 1, Faculté de Médecine, Rennes, France[c]; Service de Pharmacologie Biologique, Hôpital Pontchaillou, Rennes, France[d]; Laboratoire de Bactériologie-Virologie, Hôpital Pontchaillou, Rennes, France[e]; Service de Chirurgie Cardio-vasculaire et Thoracique, Hôpital Pontchaillou, Rennes, France[f]; Service de Biochimie, Hôpital Pontchaillou, Rennes, France[g]

Knowledge regarding antimicrobial therapy strategies in deep sternal wound infections (DSWI) following cardiac surgery is limited. Therefore, we aimed to determine the steady-state plasma and mediastinal concentrations of oxacillin administered by continuous infusion in critically ill patients with DSWI and to compare these concentrations with the susceptibility of staphylococci recovered. A continuous infusion of oxacillin (150 to 200 mg/kg of body weight/24 h) was administered after a loading dose (50 mg/kg). Plasma and mediastinal concentrations of total and unbound oxacillin were determined 4 h after the loading dose (H4) and then at day 1 (H24) and day 2 (H48). Twelve patients were included. Nine patients exhibited bacteremia, 5 were in septic shock, 8 were positive for *Staphylococcus aureus*, and 4 were positive for coagulase-negative staphylococci. The median MIC (first to third interquartile range) was 0.25 (0.24 to 0.41) mg/liter. Median plasma concentrations of total and unbound oxacillin at H4, H24, and H48 were, respectively, 64.4 (41.4 to 78.5) and 20.4 (12.4 to 30.4) mg/liter, 56.9 (31.4 to 80.6) and 21.7 (6.5 to 27.3) mg/liter, and 57.5 (32.2 to 85.1) and 20 (14.3 to 35.7) mg/liter. The median mediastinal concentrations of total and unbound oxacillin at H4, H24, and H48 were, respectively, 2.3 (0.7 to 25.9) and 0.9 (<0.5 to 15) mg/liter, 29.1 (19.7 to 38.2) and 12.6 (5.9 to 19.8) mg/liter, and 31.6 (14.9 to 42.9) and 17.1 (6.7 to 26.7) mg/liter. High-dose oxacillin delivered by continuous infusion is a valuable strategy to achieve our pharmacokinetic target (4× MIC) at the site of action at H24. But concerns remain in cases of higher MICs, emphasizing the need for clinicians to obtain the MICs for the bacteria and to monitor oxacillin concentrations, especially the unbound forms, at the target site.

Deep sternal wound infections (DSWI) following cardiac surgery, also called poststernotomy mediastinitis, are associated with significantly lengthened hospital stays and increased morbidity and mortality and, therefore, additional expenses (1–4). First-line therapy is associated with surgical debridement and antimicrobial therapy. *Staphylococcus* species were the primary causative organisms found in several cohort studies (2, 3, 5, 6). When the staphylococci are methicillin sensitive, β-lactams are the drugs of choice, in association with an aminoglycoside. Unfortunately, no recommendations are available in the context of DSWI on the type of β-lactams, the adequate dose, or the rhythm of administration. Because β-lactams are time-dependent antibiotics, efficacy is related to the time the antibiotic concentration is maintained above the MIC of the microorganisms ($T_{>MIC}$) (7). Concerning the penicillins, $T_{>MIC}$ of 50% is usually required to achieve the maximal bactericidal effects, differing from carbapenem and cephalosporin agents, for which 40% and 60 to 70% coverage, respectively, have been reported (8). However, some authors advocate for maintaining levels above the MIC 100% of the time to achieve greater clinical cure rates in serious infections (9). Additionally, *in vivo* and *in vitro* studies indicate that bacterial killing and microbiological success can be enhanced by achieving concentrations of 4× to 5× MIC (10, 11). Thus, continuous infusion has been proposed to maximize β-lactam efficacy by maintaining concentrations throughout the course of treatment (12, 13). In our institution, in case of DSWI caused by methicillin-susceptible *Staphylococcus*, a continuous infusion of high-dose oxacillin is initiated after a loading dose. However, although pharmacokinetics studies have demonstrated higher plasma drug concentrations than with bolus dosing, data on tissue drug concentrations are lacking (14). Additionally, American and European guidelines continue to recommend intermittent oxacillin infusion in the case of methicillin-susceptible staphylococci endocarditis or prosthetic-bone joint infections (15–18).

The objective of this study was to determine the steady-state plasma and mediastinal concentrations of oxacillin administered by continuous infusion to patients with DSWI after cardiac surgery and to compare these concentrations with the susceptibility of staphylococci recovered.

MATERIALS AND METHODS

This prospective observational study was performed in a 21-bed intensive care unit of a university hospital between November 2010 and June 2013. The local ethics committee (Comité d'Éthique du CHU de Rennes) approved the study and waived the need for written consent (Avis 10.17, 14 September 2010).

Received 25 February 2014 **Returned for modification** 12 March 2014
Accepted 24 June 2014
Published ahead of print 30 June 2014
Address correspondence to Nicolas Nesseler, nicolas.nesseler@chu-rennes.fr.

doi:10.1128/AAC.02624-14

TABLE 1 Biochemical parameters[a]

Parameter	Baseline	Day 1	Day 2	Day 7
Plasma creatinine concn (μmol/liter) (no. of patients)	152 (87–183) (12)	165 (94–185) (11)	142 (106–189) (12)	172 (132–186) (6)
Creatinine clearance (ml/min) (no. of patients)	39 (32–67) (12)	35 (31–61) (11)	42 (31–49) (12)	34 (32–47) (6)
Total proteins (g/liter) (no. of patients)	52 (50–54) (12)	55 (51–57) (11)	55 (51–63) (12)	58 (51–64) (6)
Albumin (g/liter) (no. of patients)	20 (18–25) (10)	24 (17–25) (10)	23 (15–27) (10)	14 (13–17) (4)

[a] Data expressed as medians and first and third quartile ranges.

Patient characteristics and management. All adult patients >18 years old admitted to our intensive care unit (ICU) after undergoing operations for DSWI after cardiac surgery with mediastinal drainage and for whom oxacillin antimicrobial therapy was indicated were eligible. Exclusion criteria included pregnancy and known allergies to β-lactams.

The surgical management followed was a primary closed-drainage technique with small multiperforated rigid 9-French catheters (Redon catheters) (19, 20). Each catheter was connected to a bottle in which a strong negative pressure was maintained. Operative mediastinal tissue and fluids were systematically cultured, and a probabilistic antimicrobial therapy associated with vancomycin and gentamicin was initiated. Two times a week, the effluents collected in the bottle were cultured. When two subsequent cultures results were negative, the catheters were progressively removed.

After *Staphylococcus* methicillin susceptibility was confirmed, the patients received a loading dose of 50 mg/kg of body weight of oxacillin (Bristopen; Bristol-Myers Squib, Rueil-Malmaison, France) over a 15-min period followed by a continuous infusion of 150 to 200 mg/kg/24 h divided in three syringes of 50 ml (Luer-Lok 50-ml syringe; BD Plastipak, Franklin Lakes, New Jersey, USA) infused over a period of 8 h via an automatic pump (Orchestra, module DPS; Fresenius Kabi AG, Bad Homburg, Germany). The dose was chosen according to the French guidelines for bone and joint prosthetic device infections, assuming the sternum was involved in DSWI and steel wires were used to close the sternotomy (15). According to our local antimicrobial therapy protocol, gentamicin was also used for 5 days before switching to oral rifampin. Oxacillin was diluted in 0.9% sodium chloride. The stability of oxacillin diluted at 100 mg/ml in 0.9% sodium chloride was evaluated at room temperature (22 to 23°C) after 8 h and 24 h. Oxacillin solutions were >98% stable at 8 h and >95% at 24 h (data not shown).

Plasma and mediastinal sampling. The plasma concentrations of total and unbound oxacillin were obtained 4 h after the loading dose (H4) and then on day 1 (H24), day 2 (H48), and day 7 if the patients were still hospitalized in our ICU. With a 30- to 60-min half-life of oxacillin reported by the manufacturer, we assumed the plasma oxacillin steady state should be reached at H4 (i.e., 4 to 5 half-lives). Simultaneously, total and unbound oxacillin levels were determined from mediastinal fluid exteriorized by the Redon catheter in the collecting bottle. The collecting bottle was changed after every sample and every day. Stability of oxacillin in mediastinal fluid at room temperature over 24 h was tested, showing a <15% decrease in the concentration (data not shown). After the first 48 h of infusion, the oxacillin dose might be modified at the discretion of the attending physician and according to the plasma drug concentrations obtained.

Measurements. The following data were collected: age, gender, height, weight, type of initial cardiac surgery, and severity of preexisting underlying disease based on McCabe's classification. The severity of illness was assessed using the sequential organ failure assessment (SOFA) score within 24 h after surgery and the simplified acute physiology score (SAPS II) within 24 h of ICU admission (21–23). The mortality at day 28 was recorded. The presence of bacteremia, septic shock, and acute respiratory distress syndrome (ARDS) was additionally recorded. The time to sterilize the mediastinal fluid (calculated as the time between the day of surgery and the day at which the collected mediastinal sample was microbiologically negative) and the need for an additional debridement surgery were also noted (6). Baseline, day 1, day 2, and day 7 (if applicable) plasma creatinine, total protein, and albumin levels were measured. Creatinine clearance (CL_{CR}) was predicted according the modification of the diet in renal disease (MDRD) formula (24).

Drug assay. Blood samples were drawn into heparinized plasma-sampling tubes. Blood samples and mediastinal fluids were centrifuged for 10 min at 3,000 × *g* and 4°C before freezing at −80°C until analysis. The storage time of the samples did not exceed 15 days. Free plasma and mediastinal fractions of oxacillin were separated by ultrafiltration using a Centrifree device (Millipore Corporation, Bedford, MA, USA), as previously described (25). Total and free oxacillin concentrations were obtained by liquid chromatography-tandem mass spectrometry (LC-MS/MS). The extraction method for oxacillin consisted of protein precipitation with acetonitrile. Separation was achieved with an Atlantis T3 column (3 μm, 2.1 by 100 mm) (Waters, Milford, MA, USA) using cefazolin as an internal standard. The method is accurate and reproducible; all intra- and interday precision and accuracy values were <5%. The assay is linear over a range from 0.5 to 250 μg/ml, the limit of quantification is 0.5 μg/ml, and the limit of detection is 0.2 μg/ml.

MIC determination. The MICs of the staphylococci were determined by the Etest (bioMérieux, Marcy l'Etoile, France). According to the recommendations of the French Society of Microbiology (www.sfm-microbiologie.org) or the European Committee on Antimicrobial Susceptibility Testing (EUCAST) (www.eucast.org), *Staphylococcus aureus* was considered susceptible to oxacillin if the MIC was ≤2 mg/liter and resistant if the MIC was >2 mg/liter. Coagulase-negative staphylococci were considered susceptible to oxacillin if the MIC was ≤0.25 mg/liter, resistant if the MIC was >2 mg/liter, and intermediate if the MIC was between these two concentrations. In the last case, if penicillin-binding protein (PBP) 2a expression was not observed, the staphylococcus was considered susceptible to oxacillin.

Statistical analysis. Statistical analysis was performed using the computer open source software program R 2.15.2, from the R Foundation (Vienna, Austria). Quantitative data were expressed as medians and first- and third-quartile ranges, whereas categorical data were expressed as absolute values and percentages.

RESULTS

Twelve patients (1 woman and 11 men) were included in the study. The median age was 73 (65 to 76) years old, median weight was 87 (79 to 95) kg, and median height was 172 (170 to 175) cm. The McCabe classification included 5 and 7 cases of A and B, respectively. The type of initial cardiac surgery included 5 cases of coronary bypass graft (CABG), 3 cases of valve surgery, 2 cases of CABG and valve surgery, and 2 cases of thoracic aortic surgery. The median time between the hospitalization for the cardiac surgery and the surgery for DSWI was 13 (12 to 20) days. The severity of illness as assessed by SAPS II was 38 (35 to 43), and the SOFA score was 6 (3 to 10). Nine patients exhibited at least one episode of bacteremia, 5 patients were in septic shock, and 4 patients met ARDS criteria. Eleven patients were alive at day 28. The plasma creatinine levels, CL_{CR} values, and total protein and albumin levels at baseline, day 1, day 2, and day 7 are summarized in Table 1. The causative organisms included *Staphylococcus aureus* in 8 patients and coagulase-negative staphylococci in 4 patients. The median MIC (first to third interquartile range) was 0.25 (0.24 to 0.41)

TABLE 2 Total, free fraction, and unbound plasma oxacillin concentrations

Patient no.	Day 1 H4			Day 1 H24			Day 2 H48		
	Total (mg/liter)	Unbound (mg/liter)	Free fraction (%)	Total (mg/liter)	Unbound (mg/liter)	Free fraction (%)	Total (mg/liter)	Unbound (mg/liter)	Free fraction (%)
1	63.7	16.9	26.5	79.3	21.9	27.6	75.8	17.2	22.7
2	43.8	14.0	31.9	57.7	6.9	12.0	30.4	9.0	29.6
3	65.1	29.6	45.5	33.4	15.8	47.3	59.4	31.8	53.5
4	30.1	4.4	14.5	25.6	4.7	18.2	31.2	5.5	17.7
5	101.2	44.7	44.2	104.4	52.8	50.5	119.4	73.7	61.7
6	87.7	32.9	37.5	56.0	28.5	50.9	55.5	23.1	41.6
7	50.1	21.5	42.9	49.2	27.0	54.8	32.6	16.0	49.1
8	75.4	23.5	31.2	61.9	21.5	34.8	112.8	47.5	42.1
9	20.6	4.1	19.9	21.1	4.0	18.8	19.0	3.7	19.5
10	34.5	7.7	22.4	21.2	5.3	25.2	55.3	16.6	30.1
11	124.9	73.5	58.8	150.2	73.1	48.7	124.5	59.5	47.8
12	69.8	19.4	27.8	84.5	26.7	31.6	60.9	22.8	37.5
Median	64.4	20.4	31.5	56.9	21.7	33.2	57.5	20.0	39.5
IQR1[a]	41.4	12.4	25.5	31.4	6.5	23.6	32.2	14.3	27.9
IQR3	78.5	30.4	43.2	80.6	27.3	49.1	85.1	35.7	48.1

[a] IQR1 and IQR3, first and third interquartile ranges, respectively.

mg/liter. The median dose of infused oxacillin was 150 (141 to 168) mg/kg/24 h. The dosage was decreased after day 2 in 4 patients by the attending physicians according to the plasma drug concentrations obtained. The median time to obtain mediastinal sterilization ($n = 11$) was 8 (6 to 16) days. Two patients needed an additional debridement surgery to obtain surgical site sterilization and one because of Gram-negative bacilli superinfection.

The plasma and mediastinal concentrations of total, unbound, and free fraction oxacillin at H4, H24, and H48 are presented in Tables 2 and 3. The drug penetration ratios (i.e., mediastinal concentrations to plasma concentrations) are shown in Table 4. The relationship between plasma and mediastinum unbound oxacillin concentrations at H4, H24, and H48 with 4× MIC recovered and 4× MIC breakpoint of staphylococci are illustrated in Fig. 1 and 2.

On day 7, the plasma concentrations ($n = 6$) of total, unbound, and free-fraction oxacillin (%) were 37.8 (17.5 to 54.4) mg/liter, 26.9 (13.2 to 48.2) mg/liter, and 25.6% (14.9 to 48.5%), respectively. On day 7, the mediastinal concentrations ($n = 6$) of total, unbound, and free-fraction oxacillin were, respectively, 31.1 (12.6 to 48.9) mg/liter, 19.2 (4.5 to 34.4) mg/liter, and 54.9% (38.9 to 70.5%).

No significant correlation was observed between the plasma concentrations at H24 and the total daily dose (dose/kg) ($r^2 = 0.005$, $P = 0.71$). A significant correlation was observed between plasma and mediastinal H24 concentrations of total ($r^2 = 0.62$, $P < 0.001$) and unbound oxacillin ($r^2 = 0.636$, $P < 0.001$). No significant relationship was observed between the plasma concentrations of unbound oxacillin and levels of albumin ($r^2 = 0.1$, $P = 0.14$) or creatinine ($r^2 = 0.23$, $P = 0.14$). A significant, but weak,

TABLE 3 Total, free fraction, and unbound mediastinal oxacillin concentrations

Patient no.	Day 1 H4			Day 1 H24			Day 2 H48		
	Total (mg/liter)	Unbound (mg/liter)	Free fraction (%)	Total (mg/liter)	Unbound (mg/liter)	Free fraction (%)	Total (mg/liter)	Unbound (mg/liter)	Free fraction (%)
1	0.5	<0.5	ND[a]	25.7	9.7	37.7	42.9	18.0	42.0
2	5.5	1.3	24.0	43.2	18.5	42.8	15.1	6.9	45.7
3	1.7	1.3	76.5	29.5	17.8	60.5	37.2	23.8	63.8
4	<0.5	<0.5	ND	17.9	5.3	29.9	21.6	7.1	32.7
5	<0.5	<0.5	ND	37.7	15.3	40.5	83.4	57.6	69.1
6	0.8	<0.5	ND	39.9	29.5	73.8	42.9	35.4	82.6
7	39.5	20.7	52.3	37.2	23.8	64.1	30.5	20.2	66.2
8	3.1	0.9	29.4	28.7	10.0	34.9	32.7	16.1	49.3
9	0.7	<0.5	ND	7.8	2.4	30.0	1.0	<0.5	30.6
10	1.6	0.8	47.8	19.5	6.0	30.9	14.5	4.8	33.1
11	43.3	18.3	42.1	86.8	45.5	52.4	105.4	65.5	62.2
12	32.7	15.0	45.9	19.8	4.7	23.5	13.7	5.9	43.2
Median	2.3	0.9	42.1	29.1	12.6	39.1	31.6	17.1	47.5
IQR1[b]	0.7	<0.5	29.4	19.7	5.9	30.7	14.9	6.7	39.7
IQR3	25.9	15.0	47.8	38.2	19.8	54.4	42.9	26.7	64.4

[a] ND, not determined.
[b] IQR1 and IQR3, first and third interquartile ranges, respectively.

TABLE 4 Drug penetration ratios (mediastinal concentrations to plasma concentrations)

Patient no.	Total oxacillin concentration ratio			Unbound oxacillin concentration ratio		
	Day 1 H4	Day 1 H24	Day 2 H48	Day 1 H4	Day 1 H24	Day 2 H48
1	0.01	0.32	0.57	—[a]	0.44	1.05
2	—	0.75	0.50	0.09	2.68	0.77
3	0.03	0.88	0.63	0.04	1.13	0.75
4	—	0.70	0.69	—	1.13	1.29
5	—	0.36	0.70	—	0.29	0.78
6	0.01	0.71	0.77	—	1.04	1.53
7	0.79	0.76	0.94	0.96	0.88	1.26
8	0.04	0.46	0.29	0.04	0.47	0.34
9	0.03	0.37	0.05	—	0.60	—
10	0.05	0.92	0.26	0.10	1.13	0.29
11	0.35	0.58	0.85	0.25	0.62	1.10
12	0.47	0.23	0.22	0.77	0.18	0.26
Median	0.04	0.64	0.60	0.10	0.75	0.78
IQR1[b]	0.03	0.37	0.28	0.07	0.46	0.54
IQR3	0.35	0.75	0.72	0.51	1.13	1.18

[a] —, not calculated.
[b] IQR1 and IQR3, first and third interquartile ranges, respectively.

correlation was observed between the plasma concentrations of unbound oxacillin and CL_{CR} ($r^2 = 0.27$, $P = 0.003$). A significant correlation was observed between the free fraction of plasma oxacillin at steady state and albumin levels. The free fraction increased when the albumin level decreased ($r^2 = 0.46$, $P < 0.001$).

DISCUSSION

The present study revealed that at H24, continuous infusion of oxacillin at 150 to 200 mg/kg/day after a loading dose of 50 mg/kg was sufficient to achieve bactericidal concentrations, i.e., concentrations in excess of 4× to 5× MIC of unbound oxacillin at the site

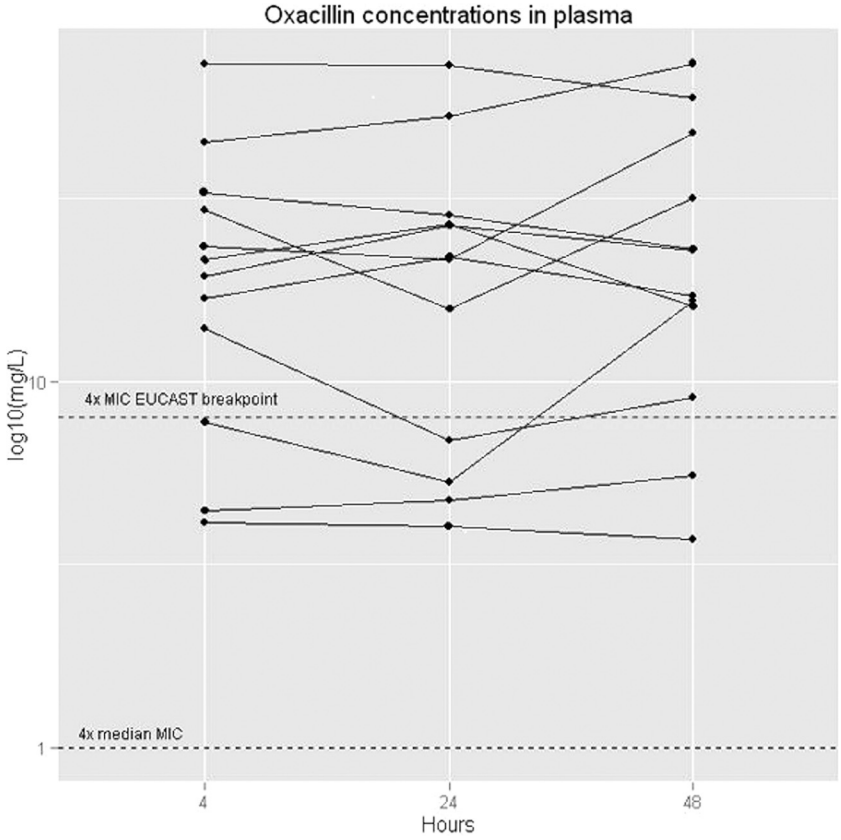

FIG 1 Relationship between unbound oxacillin plasma concentrations at H4, H24, and H48 with 4× MIC for staphylococci recovered and 4× breakpoint MIC for staphylococci.

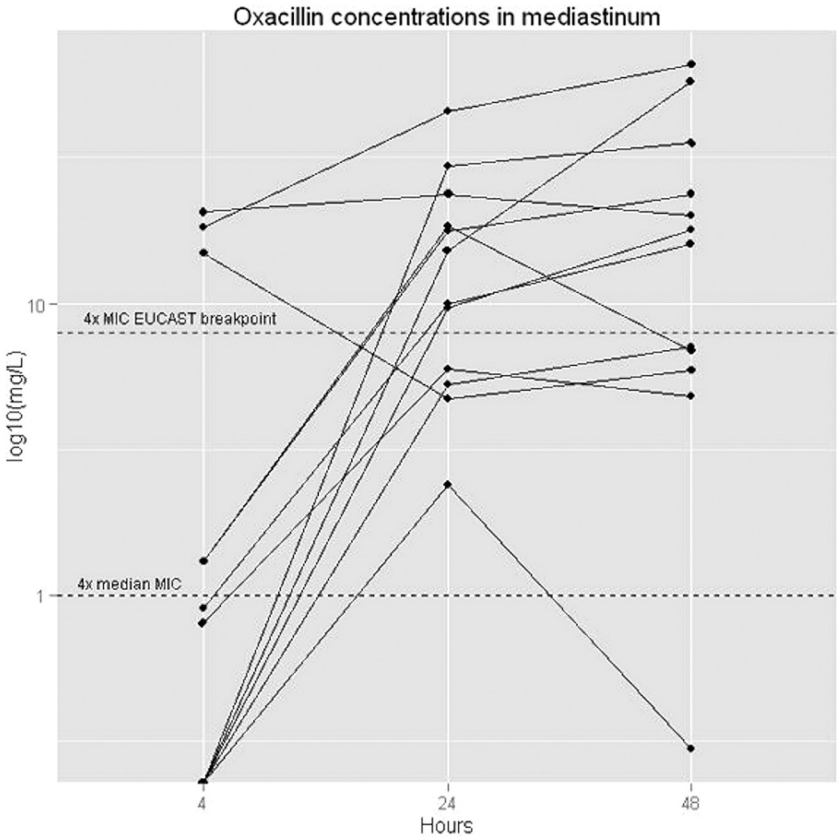

FIG 2 Relationship between unbound oxacillin mediastinal concentrations at H4, H24, and H48 with 4× MIC for staphylococci recovered and 4× breakpoint MIC for staphylococci.

of action if we considered the susceptibility of staphylococci recovered in our patients. Indeed, for all patients (except one at H48), the concentrations of unbound oxacillin were sufficiently high at H24 and H48. However, if we considered the reported MIC breakpoint for the staphylococci susceptibility of 2 mg/liter defined by the French Society of Microbiology or the European Committee on Antimicrobial Susceptibility Testing (EUCAST) (www.eucast.org), the objectives were achieved in only 8 patients at H24 and 7 patients at H48.

Interestingly, at H4 the oxacillin steady state was not reached in the mediastinum, contrary to the plasma. Therefore, the oxacillin bactericidal concentrations at the target site were recovered in only 3 patients, calling into question the sufficiency of the loading dose chosen. This issue is critical when considering that the timing of antimicrobial therapy administration is associated with outcomes in severe sepsis and septic shock (26). A higher loading dose might eventually be proposed to achieve bactericidal concentrations more quickly, but the efficiency of such a measure needs to be demonstrated. Moreover, peak concentrations after a loading dose should be measured to determine that toxic concentrations were not attained. In order to specify this issue, we made an attempt at modeling the data set through nonlinear mixed-effect models. However, the data were very sparse and were not originally designed for such an analysis. As a result, the parameter estimates proved very sensitive to the assumptions made in the modeling, and the variability was very high. In addition, there was large interindividual variability in this very sick population, making any conclusions or extrapolation to different dose regimens hazardous. However, the analysis did suggest that the distribution to the mediastinal tissues takes several hours, despite heavy loading doses in the plasmatic compartment. In further studies, it would be worthwhile to obtain additional samples during the distribution phase to better estimate the volume of distribution and the distribution to the mediastinal tissue. Such a new data set would allow the determination of whether increasing the dose regimens would achieve bactericidal concentrations in the mediastinal tissue within the recommended time frame, or whether a loading dose directly in the mediastinal tissue during the surgery would be more relevant.

The patients included in our study were critically ill, and 5 patients were in septic shock. All of the patients exhibited hypoalbuminemia (<25 g/liter), a state frequently observed in critically ill patients (27). Hypoalbuminemia resulted in an increased free fraction compared with that reported by the manufacturer (approximately 35% versus 10%). Changes in the volume of distribution and the clearance of antibiotics have been reported in critically ill patients, which may affect the antibiotic concentrations at the target site, notably for hydrophilic antibiotics like β-lactams (28). Moreover, microdialysis studies indicated that antibiotic tissular penetration is impaired in septic shock (29). Additionally, hypoalbuminemia results in a higher unbound fraction associated with increased clearance of unbound drug and greater volume of distribution (*V*). This pharmacokinetic alteration exists for highly protein-bound antibiotics, such as ceftriax-

one, oxacillin, ertapenem, and teicoplanin, and might be associated with failure to achieve pharmacokinetic-pharmacodynamic targets (28, 30, 31). Although this phenomenon is well documented for other antibiotics, no data are available for oxacillin (30, 32–34). A recent study on the pharmacokinetics of flucloxacillin, a highly protein-bound isoxazolyl penicillin, was conducted in critically ill patients with hypoalbuminemia without impaired renal function (35). Flucloxacillin was delivered by intermittent infusion of 1 to 2 g every 4 to 6 h, and the authors reported that within 4 h after administration, the plasma unbound concentrations of 6/10 patients fell below 1 mg/liter. Additionally, Monte Carlo simulations suggested that a protocol of high-dose continuous infusion after a loading dose, similar to the protocol we followed, might achieve an aggressive pharmacokinetics target, i.e., 4× to 5× MIC 100% of the time with respect to the staphylococci clinical susceptibility breakpoint (35). In our study, despite the delivery modalities of oxacillin, the plasma-unbound concentrations were below 4× MIC, with respect to the staphylococci clinical susceptibility breakpoint, in 4 patients at H24 and in 1 patient at H48, challenging this hypothesis. Interestingly, most of our patients exhibited impaired renal function, but no significant relationship was observed between oxacillin concentrations and creatinine levels or only a weak relationship with CL_{CR}. The phenomenon can be explained by the primary biliary elimination characterizing oxacillin (36, 37).

In clinical settings, a recent retrospective study suggested that continuous oxacillin infusion was a suitable alternative to intermittent infusion, with better microbiological outcomes in infective endocarditis caused by methicillin-susceptible *Staphylococcus* (38). In the same way, continuous oxacillin infusion was retrospectively found to be associated with good success rates in the treatment of burn wound cellulitis (39).

In the absence of specific recommendations concerning antimicrobial therapy in the field, our study provides a set of additional useful information to the clinicians in charge of DSWI after cardiac surgery. Although the continuous infusion and dosing regimens chosen appear adequate in most cases, our study emphasizes the need for the physicians to obtain MICs and to monitor plasma and, if possible, tissue oxacillin concentrations. Indeed, appropriate dosing regimens are necessary to avoid therapeutic failure and/or the development of antibiotic resistance (28).

Our study exhibits several strengths. We report here for the first time, to our knowledge, the target site concentrations of oxacillin during the management of DSWI in critically ill patients. The pharmacokinetics data of this narrow-spectrum and high protein-binding penicillin are of critical interest considering the frequency of staphylococci in DSWI and the changes of pharmacokinetics in critically ill patients. Moreover, only the pharmacologically active unbound oxacillin concentrations were considered to evaluate the achievement of pharmacokinetic targets.

Some limitations, however, should be noted. First, we observed interindividual variability in pharmacokinetic values, as is frequently reported among critically ill patients (32). Second, the significance of the microbiological and clinical outcome data should be analyzed with caution given that our cohort size remains limited and the study was not designed to evaluate the clinical cure rates. Additionally, given the number of patients included, we cannot exclude the possibility that the lack of relations between the various parameters is related to sample size as opposed to no real effect being present. High free fractions were reported in our study mainly related to hypoalbuminemia, but unbound oxacillin concentrations were determined by ultrafiltration and not by equilibrium dialysis, which is the current standard. However, other studies determined the unbound concentration of β-lactams (including flucloxacillin and dicloxacillin) using the ultracentrifugation method, and the stability of our method was checked by repeating the technique several times on the same sample to ensure reliability (40–42).

In conclusion, high-dose oxacillin delivered by continuous infusion after a loading dose is a valuable strategy to achieve our pharmacokinetic target at the site of action. However, the range of MICs recovered in our patients was rather low, and in cases of higher MICs (i.e., 2 mg/liter), the pharmacokinetic target at the site of action would not have been achieved. Moreover, higher loading doses would have likely resulted in achieving bactericidal concentrations earlier. These observations emphasize the need for the clinicians to obtain the MIC of the bacteria and to monitor the antibiotic concentrations, especially the unbound forms, at the target site, if possible. More studies are needed to confirm whether such a strategy would be associated with higher clinical cure rates and better outcomes.

ACKNOWLEDGMENTS

We gratefully thank Emmanuelle Comets (INSERM CIC 1414, Rennes, France; INSERM UMR1137, IAME, Université Paris Diderot, Paris, France) for assistance in modeling.

We declare no conflicts of interest.

We received no funding for this study.

REFERENCES

1. **Bennett-Guerrero E, Ferguson TB, Jr, Lin M, Garg J, Mark DB, Scavo VA, Jr, Kouchoukos N, Richardson JB, Jr, Pridgen RL, Corey GR.** 2010. Effect of an implantable gentamicin-collagen sponge on sternal wound infections following cardiac surgery: a randomized trial. JAMA **304:**755–762. http://dx.doi.org/10.1001/jama.2010.1152.
2. **Chen LF, Arduino JM, Sheng S, Muhlbaier LH, Kanafani ZA, Harris AD, Fraser TG, Allen K, Corey GR, Fowler VG, Jr.** 2012. Epidemiology and outcome of major postoperative infections following cardiac surgery: risk factors and impact of pathogen type. Am. J. Infect. Control **40:**963–968. http://dx.doi.org/10.1016/j.ajic.2012.01.012.
3. **Eklund AM, Lyytikainen O, Klemets P, Huotari K, Anttila VJ, Werkkala KA, Valtonen M.** 2006. Mediastinitis after more than 10,000 cardiac surgical procedures. Ann. Thorac. Surg. **82:**1784–1789. http://dx.doi.org/10.1016/j.athoracsur.2006.05.097.
4. **Fowler VG, Jr, O'Brien SM, Muhlbaier LH, Corey GR, Ferguson TB, Peterson ED.** 2005. Clinical predictors of major infections after cardiac surgery. Circulation **112:**I358–I365.
5. **Fakih MG, Sharma M, Khatib R, Berriel-Cass D, Meisner S, Harrington S, Saravolatz L.** 2007. Increase in the rate of sternal surgical site infection after coronary artery bypass graft: a marker of higher severity of illness. Infect. Control Hosp. Epidemiol. **28:**655–660. http://dx.doi.org/10.1086/518347.
6. **Trouillet JL, Vuagnat A, Combes A, Bors V, Chastre J, Gandjbakhch I, Gibert C.** 2005. Acute poststernotomy mediastinitis managed with debridement and closed-drainage aspiration: factors associated with death in the intensive care unit. J. Thorac. Cardiovasc. Surg. **129:**518–524. http://dx.doi.org/10.1016/j.jtcvs.2004.07.027.
7. **Drusano GL.** 2004. Antimicrobial pharmacodynamics: critical interactions of 'bug and drug.' Nat. Rev. Microbiol. **2:**289–300. http://dx.doi.org/10.1038/nrmicro862.
8. **Craig WA.** 1998. Pharmacokinetic/pharmacodynamic parameters: rationale for antibacterial dosing of mice and men. Clin. Infect. Dis. **26:**1–10. http://dx.doi.org/10.1086/516284.
9. **McKinnon PS, Paladino JA, Schentag JJ.** 2008. Evaluation of area under the inhibitory curve (AUIC) and time above the minimum inhibitory concentration (T>MIC) as predictors of outcome for cefepime and cef-

tazidime in serious bacterial infections. Int. J. Antimicrob. Agents **31:**345–351. http://dx.doi.org/10.1016/j.ijantimicag.2007.12.009.
10. **Mouton JW, den Hollander JG.** 1994. Killing of *Pseudomonas aeruginosa* during continuous and intermittent infusion of ceftazidime in an *in vitro* pharmacokinetic model. Antimicrob. Agents Chemother. **38:**931–936. http://dx.doi.org/10.1128/AAC.38.5.931.
11. **Tam VH, McKinnon PS, Akins RL, Rybak MJ, Drusano GL.** 2002. Pharmacodynamics of cefepime in patients with Gram-negative infections. J. Antimicrob. Chemother. **50:**425–428. http://dx.doi.org/10.1093/jac/dkf130.
12. **Dulhunty JM, Roberts JA, Davis JS, Webb SA, Bellomo R, Gomersall C, Shirwadkar C, Eastwood GM, Myburgh J, Paterson DL, Lipman J.** 2013. Continuous infusion of beta-lactam antibiotics in severe sepsis: a multicenter double-blind, randomized controlled trial. Clin. Infect. Dis. **56:**236–244. http://dx.doi.org/10.1093/cid/cis856.
13. **Falagas ME, Tansarli GS, Ikawa K, Vardakas KZ.** 2013. Clinical outcomes with extended or continuous versus short-term intravenous infusion of carbapenems and piperacillin/tazobactam: a systematic review and meta-analysis. Clin. Infect. Dis. **56:**272–282. http://dx.doi.org/10.1093/cid/cis857.
14. **Roberts JA, Paratz JD, Lipman J.** 2008. Continuous infusion of beta-lactams in the intensive care unit—best way to hit the target? Crit. Care Med. **36:**1663–1664. http://dx.doi.org/10.1097/CCM.0b013e3181704625.
15. **Société de Pathologie Infectieuse de Langue Française (SPILF), Collège des Universitaires de Maladies Infectieuses et Tropicales (CMIT), Groupe de Pathologie Infectieuse Pédiatrique (GPIP), Société Française d'Anesthésie et de Réanimation (SFAR), Société Française de Chirurgie Orthopédique et Traumatologique (SOFCOT), Société Française d'Hygiène Hospitalière (SFHH), Société Française de Médecine Nucléaire (SFMN), Société Française de Médecine Physique et de Réadaptation (SOFMER), Société Française de Microbiologie (SFM), Société Française de Radiologie (SFR-Rad), Société Française de Rhumatologie (SFR-Rhu).** 2010. Recommendations for bone and joint prosthetic device infections in clinical practice (prosthesis, implants, osteosynthesis). Societe de Pathologie Infectieuse de Langue Francaise. Med. Mal. Infect. **40:**185–211. http://dx.doi.org/10.1016/j.medmal.2009.12.009.
16. **Baddour LM, Wilson WR, Bayer AS, Fowler VG, Jr, Bolger AF, Levison ME, Ferrieri P, Gerber MA, Tani LY, Gewitz MH, Tong DC, Steckelberg JM, Baltimore RS, Shulman ST, Burns JC, Falace DA, Newburger JW, Pallasch TJ, Takahashi M, Taubert KA.** 2005. Infective endocarditis: diagnosis, antimicrobial therapy, and management of complications. A statement for healthcare professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, and the Councils on Clinical Cardiology, Stroke, and Cardiovascular Surgery and Anesthesia, American Heart Association. Endorsed by the Infectious Diseases Society of America. Circulation **111:**e394–e434. http://dx.doi.org/10.1161/CIRCULATIONAHA.105.165564.
17. **Habib G, Hoen B, Tornos P, Thuny F, Prendergast B, Vilacosta I, Moreillon P, de Jesus Antunes M, Thilen U, Lekakis J, Lengyel M, Muller L, Naber CK, Nihoyannopoulos P, Moritz A, Zamorano JL.** 2009. Guidelines on the prevention, diagnosis, and treatment of infective endocarditis (new version 2009): the Task Force on the Prevention, Diagnosis, and Treatment of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and the International Society of Chemotherapy (ISC) for Infection and Cancer. Eur. Heart J. **30:**2369–2413. http://dx.doi.org/10.1093/eurheartj/ehp285.
18. **Osmon DR, Berbari EF, Berendt AR, Lew D, Zimmerli W, Steckelberg JM, Rao N, Hanssen A, Wilson WR.** 2013. Diagnosis and management of prosthetic joint infection: clinical practice guidelines by the Infectious Diseases Society of America. Clin. Infect. Dis. **56:**e1–e25. http://dx.doi.org/10.1093/cid/cis803.
19. **Calvat S, Trouillet JL, Nataf P, Vuagnat A, Chastre J, Gibert C.** 1996. Closed drainage using Redon catheters for local treatment of poststernotomy mediastinitis. Ann. Thorac. Surg. **61:**195–201. http://dx.doi.org/10.1016/0003-4975(95)00921-3.
20. **Kirsch M, Mekontso-Dessap A, Houel R, Giroud E, Hillion ML, Loisance DY.** 2001. Closed drainage using Redon catheters for poststernotomy mediastinitis: results and risk factors for adverse outcome. Ann. Thorac. Surg. **71:**1580–1586. http://dx.doi.org/10.1016/S0003-4975(01)02452-3.
21. **Le Gall JR, Lemeshow S, Saulnier F.** 1993. A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study. JAMA **270:**2957–2963. http://dx.doi.org/10.1001/jama.1993.03510240069035.
22. **Vincent JL, de Mendonca A, Cantraine F, Moreno R, Takala J, Suter PM, Sprung CL, Colardyn F, Blecher S.** 1998. Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: results of a multicenter, prospective study. Working group on "sepsis-related problems" of the European Society of Intensive Care Medicine. Crit. Care Med. **26:**1793–1800.
23. **Ferreira FL, Bota DP, Bross A, Melot C, Vincent JL.** 2001. Serial evaluation of the SOFA score to predict outcome in critically ill patients. JAMA **286:**1754–1758. http://dx.doi.org/10.1001/jama.286.14.1754.
24. **Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D.** 1999. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann. Intern. Med. **130:**461–470.
25. **Seguin P, Verdier MC, Chanavaz C, Engrand C, Laviolle B, Donnio PY, Malledant Y.** 2009. Plasma and peritoneal concentration following continuous infusion of cefotaxime in patients with secondary peritonitis. J. Antimicrob. Chemother. **63:**564–567. http://dx.doi.org/10.1093/jac/dkn522.
26. **Kumar A, Roberts D, Wood KE, Light B, Parrillo JE, Sharma S, Suppes R, Feinstein D, Zanotti S, Taiberg L, Gurka D, Cheang M.** 2006. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Crit. Care Med. **34:**1589–1596. http://dx.doi.org/10.1097/01.CCM.0000217961.75225.E9.
27. **Finfer S, Bellomo R, McEvoy S, Lo SK, Myburgh J, Neal B, Norton R.** 2006. Effect of baseline serum albumin concentration on outcome of resuscitation with albumin or saline in patients in intensive care units: analysis of data from the saline versus albumin fluid evaluation (SAFE) study. BMJ **333:**1044. http://dx.doi.org/10.1136/bmj.38985.398704.7C.
28. **Roberts JA, Lipman J.** 2009. Pharmacokinetic issues for antibiotics in the critically ill patient. Crit. Care Med. **37:**840–851. http://dx.doi.org/10.1097/CCM.0b013e3181961bff.
29. **Joukhadar C, Frossard M, Mayer BX, Brunner M, Klein N, Siostrzonek P, Eichler HG, Muller M.** 2001. Impaired target site penetration of beta-lactams may account for therapeutic failure in patients with septic shock. Crit. Care Med. **29:**385–391. http://dx.doi.org/10.1097/00003246-200102000-00030.
30. **Joynt GM, Lipman J, Gomersall CD, Young RJ, Wong EL, Gin T.** 2001. The pharmacokinetics of once-daily dosing of ceftriaxone in critically ill patients. J. Antimicrob. Chemother. **47:**421–429. http://dx.doi.org/10.1093/jac/47.4.421.
31. **Verdier MC, Seguin P, Le Touvet B, Cady A, Malledant Y, Tribut O.** 2011. Ertapenem in plasma and peritoneal fluid from patients with severe intra-abdominal infections. J. Antimicrob. Chemother. **66:**1934–1936. http://dx.doi.org/10.1093/jac/dkr211.
32. **Barbot A, Venisse N, Rayeh F, Bouquet S, Debaene B, Mimoz O.** 2003. Pharmacokinetics and pharmacodynamics of sequential intravenous and subcutaneous teicoplanin in critically ill patients without vasopressors. Intensive Care Med. **29:**1528–1534. http://dx.doi.org/10.1007/s00134-003-1859-z.
33. **Burkhardt O, Kumar V, Katterwe D, Majcher-Peszynska J, Drewelow B, Derendorf H, Welte T.** 2007. Ertapenem in critically ill patients with early-onset ventilator-associated pneumonia: pharmacokinetics with special consideration of free-drug concentration. J. Antimicrob. Chemother. **59:**277–284. http://dx.doi.org/10.1093/jac/dkl485.
34. **Mimoz O, Soreda S, Padoin C, Tod M, Petitjean O, Benhamou D.** 2000. Ceftriaxone pharmacokinetics during iatrogenic hydroxyethyl starch-induced hypoalbuminemia: a model to explore the effects of decreased protein binding capacity on highly bound drugs. Anesthesiology **93:**735–743. http://dx.doi.org/10.1097/00000542-200009000-00023.
35. **Ulldemolins M, Roberts JA, Wallis SC, Rello J, Lipman J.** 2010. Flucloxacillin dosing in critically ill patients with hypoalbuminaemia: special emphasis on unbound pharmacokinetics. J. Antimicrob. Chemother. **65:**1771–1778. http://dx.doi.org/10.1093/jac/dkq184.
36. **Barza M, Weinstein L.** 1976. Pharmacokinetics of the penicillins in man. Clin. Pharmacokinet. **1:**297–308. http://dx.doi.org/10.2165/00003088-197601040-00004.
37. **Pea F, Viale P, Pavan F, Furlanut M.** 2007. Pharmacokinetic considerations for antimicrobial therapy in patients receiving renal replacement therapy. Clin. Pharmacokinet. **46:**997–1038. http://dx.doi.org/10.2165/00003088-200746120-00003.

38. **Hughes DW, Frei CR, Maxwell PR, Green K, Patterson JE, Crawford GE, Lewis JS, II.** 2009. Continuous versus intermittent infusion of oxacillin for treatment of infective endocarditis caused by methicillin-susceptible *Staphylococcus aureus*. Antimicrob. Agents Chemother. **53:** 2014–2019. http://dx.doi.org/10.1128/AAC.01232-08.
39. **Schuster KM, Wilson D, Schulman CI, Pizano LR, Ward CG, Namias N.** 2009. Continuous-infusion oxacillin for the treatment of burn wound cellulitis. Surg. Infect. (Larchmt.) **10:**41–45. http://dx.doi.org/10.1089/sur.2007.081.
40. **Briscoe SE, McWhinney BC, Lipman J, Roberts JA, Ungerer JP.** 2012. A method for determining the free (unbound) concentration of ten beta-lactam antibiotics in human plasma using high performance liquid chromatography with ultraviolet detection. J. Chromatogr. B Analyt. Technol. Biomed. Life Sci. **907:**178–184. http://dx.doi.org/10.1016/j.jchromb.2012.09.016.
41. **Roberts JA, Paul SK, Akova M, Bassetti M, De Waele JJ, Dimopoulos G, Kaukonen KM, Koulenti D, Martin C, Montravers P, Rello J, Rhodes A, Starr T, Wallis SC, Lipman J.** 2014. DALI: defining antibiotic levels in intensive care unit patients: are current beta-lactam antibiotic doses sufficient for critically ill patients? Clin. Infect. Dis. **58:**1072–1083. http://dx.doi.org/10.1093/cid/ciu027.
42. **Wong G, Briscoe S, Adnan S, McWhinney B, Ungerer J, Lipman J, Roberts JA.** 2013. Protein binding of beta-lactam antibiotics in critically ill patients: can we successfully predict unbound concentrations? Antimicrob. Agents Chemother. **57:**6165–6170. http://dx.doi.org/10.1128/AAC.00951-13.